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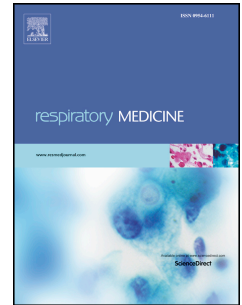
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Clinical features of sarcoidosis associated pulmonary hypertension: Results of a multi-national registry

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Clinical features of sarcoidosis associated pulmonary hypertension: results of a multi-national registry

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RPB performed all data analysis and was responsible for drafting the manuscript. RPB, OAS, AUW, EHA, DAC, EMC, EEL, PJE, and SDN all provided significant input into the writing of the manuscript. All authors contributed to patient entry and supervising data entry at each of their sites. All authors reviewed the final manuscript.

Abstract: 224

Tables: 5

Supplement Tables: 2

Figures: 6

Abstract (224 words)

Background: Pulmonary hypertension (PH) is a significant cause of morbidity and mortality in sarcoidosis. We established a multi-national registry of sarcoidosis associated PH (SAPH) patients.

Methods: Sarcoidosis patients with PH confirmed by right heart catheterization (RHC) were studied. Patients with pulmonary artery wedge pressure (PAWP) of 15 mmHg or less and a mean pulmonary artery pressure (mPAP) \geq 25 Hg were subsequently analyzed. Data collected included hemodynamics, forced vital capacity (FVC), diffusion capacity of carbon monoxide (DL_{CO}), chest x-ray, and six-minute walk distance (6MWD).

Results: A total of 176 patients were analyzed. This included 84 (48%) cases identified within a year of entry into the registry and 94 (53%) with moderate to severe PH. There was a significant correlation between DL_{CO} percent predicted (% pred) and mPAP ($Rho = -0.228$, $p = 0.0068$) and pulmonary vascular resistance (PVR) ($Rho = -0.362$, $p < 0.0001$). PVR was significantly higher in stage 4 disease than in stage 0 or 1 disease ($p < 0.05$ for both comparisons). About two-thirds of the SAPH patients came from the United States (US). There was a significant difference in the rate of treatment between US (67.5%) versus non-US (86%) (Chi Square 11.26, $p = 0.0008$) sites.

Conclusions The clinical features of SAPH were similar across multiple centers in the US, Europe, and the Middle East. The severity of SAPH was related to reduced DLCO. There were treatment differences between the US and non-US centers.

Key words: sarcoidosis associated pulmonary hypertension, epidemiology, sarcoidosis

Introduction

Sarcoidosis associated pulmonary hypertension (SAPH) is associated with significant morbidity and an increased mortality¹⁻⁴. The incidence of SAPH in a general sarcoidosis clinic varies between 5 to 20%⁵⁻⁷. The lower rates have been reported in general sarcoidosis clinics⁵, while higher rates have been reported from tertiary referral clinics⁶. Over half of sarcoidosis patients with persistent dyspnea or listed for lung transplant have SAPH^{1;8;9}. Despite increased recognition of SAPH over the past decade, there are still significant gaps in knowledge about this condition and there are no direct comparisons between the features or treatment of SAPH in various parts of the world.

To gather more knowledge about the disease, we established an observational Registry for Sarcoidosis Associated Pulmonary Hypertension (ReSAPH) to prospectively collect data on patients with incident or prevalent SAPH. The registry was designed to collect information regarding the initial presentation and subsequent clinical course of SAPH patients from sarcoidosis centers across the world. Data collected included hemodynamic measures to assess severity of pulmonary hypertension, pulmonary function testing and chest imaging to characterize the underlying pulmonary involvement, and six-minute walk distance (6MWD). We also collected information on treatment for the pulmonary hypertension. We now report the analysis of the demographics, disease course, and management of the first 176 patients with pre-capillary SAPH and compare those results to pulmonary sarcoidosis patients without pulmonary hypertension. We also compared the clinical features of SAPH for United States (US) and non-US sites.

Materials and Methods

Patients with a diagnosis of sarcoidosis based on the ATS/ERS/WASOG criteria and hemodynamic diagnosis of PH were enrolled in an eleven center observational registry¹⁰. The registry was initiated in October 2011. All patients were required to have at least one right heart catheterization (RHC) demonstrating a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. Incident cases were defined as the diagnosis of PH within one year of entry into the registry, whereas prevalent cases were diagnosed more than a year prior. Patients were recruited from individual clinic patients. There was no advertising or other efforts to recruit all SAPH patients within each geographic area of the individual clinic. The overall study was designed to recruit 200 patients with half of cases to be incident cases. This sample size was based on prior single center studies of SAPH patients. All information was recorded in a secure web-based electronic database (REDCap)¹¹. Each investigator had obtained local institutional review board approval prior to entering any patient into the database. The study is registered at ClinTrials.gov at number NCT01467791. The authors used the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) checklist in preparing this report.

For each patient, the first RHC identifying PH was recorded. Values recorded included the mean right atrial (RA) pressure, systolic, diastolic, and mPAP, the pulmonary artery wedge pressure (PAWP), cardiac output (CO) by thermodilution, and cardiac index (CI). Pulmonary vascular resistance (PVR) was calculated and reported in Wood units.

At time of entry into the study, all patients underwent a history and focused physical examinations. Age, gender, self-declared race, organ involvement using standard criteria^{12,13}, duration of sarcoidosis and SAPH were recorded. Pulmonary function studies data obtained included forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), the ratio of FEV₁ to FVC, (FEV₁/FVC) and diffusion capacity of carbon monoxide (DL_{CO}) with % predicted values using the local laboratory formulas correcting for race and hemoglobin. PH-specific therapy was recorded. When available, the most recent chest x-ray at the time of entry into the study was reviewed and staged using Scadding criteria¹⁴.

For the US sites and one site in Europe (Rotterdam), additional information was obtained on all patients enrolled. Information collected included 6MWD using a standard protocol^{15,16}, oxygen saturation and Borg score¹⁵ initially and at the end of walking, as well as the use and rate of supplemental oxygen during the test.

Statistics

Correlations between variables were calculated using Spearman rank correlation using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014). Kruskal Wallis testing was performed to analyze for variance between groups. Chi square was performed to compare factors. Comparison between groups were made using Mann Whitney U test. A p value of less than 0.05 was considered significant.

Results

At the time of this analysis in May 2017, 216 patients were enrolled. Supplement Table 1 lists the sites, principal investigator at each site, and number of patients enrolled. Seven of the eleven sites (five from US and two non US) enrolled 19 or more patients. The hemodynamic data of all these patients was reviewed and 176 patients with documented $mPAP \geq 25$ mm Hg and a PAWP of ≤ 15 mmHg constituted the final study cohort (Figure 1). Of these 176 patients, the diagnosis of SAPH had been confirmed by RHC within one year of study entry in 84 cases (incident cases). There was no significant difference between the hemodynamic features of the incident cases compared to the prevalent cases (Supplement Table 2). All further analyses were performed on the combined group. Table 1 summarizes the demographic features of the total population. There were 81 (46.0%) cases with moderate to severe pulmonary hypertension¹⁶ as defined by a $mPAP > 35$ mm Hg.

Figure 2A demonstrates the $mPAP$ for the whole group. Figure 2B shows the PVR for the group. There was no relationship between FVC % predicted or any other spirometric value and the pulmonary hemodynamics. There was a significant correlation between DL_{CO} % predicted and $mPAP$ (Figure 3A, $Rho = -0.228$, $p = 0.0068$) and PVR (Figure 3B, $Rho = -0.362$, $p < 0.0001$). There was no correlation between FVC % predicted and either $mPAP$ ($Rho = 0.0179$, $p > 0.05$) or PVR ($Rho = 0.126$, $p > 0.05$).

The chest x-ray was staged using Scadding¹⁴ criteria was available in 135 patients. Figure 4 demonstrates the $mPAP$ and PVR for the 89 patients with stage 4 chest x-ray versus the 46 with other stages. There was a significant difference between groups in regards to their PVR measurements

(Kruskal-Wallis test, $p=0.034$) with stage 4 patients having significantly higher values than either stage 0 or 1 patients ($p<0.05$ for both comparisons) with no difference in mPAP.

Based on WASOG criteria for organ involvement¹², patients were classified as either lung involvement only (80 patients) versus those with extra-pulmonary disease (96 patients). There was no significant difference in the mPAP pressure for those with lung only disease (36 (25-60) mm Hg) versus systemic disease (34 (25-62) mm Hg) or for PVR (lung only (5.44 (1.94, 18.3) Wood units) versus systemic disease (5.5 (1.85, 20.49) Wood units)).

Of the 176 patients studied, 126 came from US centers and 50 from European or Middle Eastern centers. Table 2 describes the characteristics of the patients in both groups. There was no significant difference between groups in terms of age or gender. There were significant differences in the self-declared race for the two groups (Chi Square=64.804, $p<0.0001$). For the reported hemodynamics, there was no difference in mPAP, but PVR was significantly higher for the non- US group ($p=0.0079$).

There was no significant difference for spirometry or DL_{co}% predicted between the two groups. We compared those who were white versus black, regardless of country of origin. There was no difference in mPAP or PVR between the 57 white patients versus the 96 black patients (data not shown). There was also no difference in FVC or FEV₁ % predicted between whites versus blacks (data not shown). However, white patients had a lower FEV₁/FVC ratio (66 % (21-91), median [range]) than blacks (74% [27-91], $p=0.0069$). The DL_{co}% predicted was significantly lower for blacks (31% [3-69]) than whites (43.3% [14.2-94], $p=0.0020$).

Table 1 also includes the results of 142 patients who underwent six minute walk testing at time of entry into the study. The median 6MWD was 305 meters (range 11-610 meters). Most patients desaturated during the test, with a median degree of desaturation of 5%. Figure 5 shows the distribution of the desaturation. A correlation between 6MWD and other features is summarized in Table 3. This univariate analysis identified six features with a p value of less than 0.05: end of walk Borg, sPAP, dPAP, mPAP, PVR, and DL_{co}% predicted. Multi-variate analysis of these six features detected three independent features: end of walk Borg (p=0.0014), sPAP (p=0.0047, and DL_{co}% predicted (p=0.0002). There was a significant correlation between the DL_{co}% predicted and 6MWD (Figure 6: rho=0.380, p<0.0001).

Table 4 compares the therapy at time of entry into the study for US versus non-US sites. Nearly a third of US patients were not treated, while only four non-US patients were not on any therapy at time of entry into the registry (Chi square=11.26, p=0.0008). The US patients were more likely to be on current therapy with a calcium channel blocker than the non-US sites (Chi square 4.002, p=0.0454), but only seven were receiving a calcium channel blocker as monotherapy. There was no significant difference in endothelin receptor blockers or prostanoids usage. The relatively low rate of usage of newer agents such as macitentan and riociguat probably reflects that most patients were started on therapy prior to the availability of these drugs.

We compared the rate of treatment for mild versus moderate to severe pulmonary hypertension (mPAP>35 mm Hg). The results are summarized in Table 5. For the US sites, 55 of 126 (43.7%) had moderate to severe pulmonary hypertension versus 26 of 50 (52%) of the non-US sites (Chi

square=0.696, $p>0.05$). For both US and non-US sites, there was no significant difference in the rate of treatment for mild versus moderate to severe PH. When we compared the rate of treatment for US versus non-US sites, we still found a significant difference in rate of treatment for both mild and moderate to severe PH.

Discussion

Pulmonary hypertension is a recognized complication of sarcoidosis^{1;17;18}. However, there is still limited information regarding the clinical presentation and the role of therapy for this malady. Because of the relatively low incidence, most reports are derived from single center experiences^{6;8}. This current study prospectively obtained information on 176 RHC-confirmed cases of SAPH from the US, Europe, and the Middle East. This multinational approach provides a global perspective and insight into features of SAPH. It also identified regional differences, which were most apparent with regards to the implementation of treatment. Half of the patients had been diagnosed with SAPH within a year of time of entry into the registry, however there was no significant difference between these incident cases and the remaining prevalent cases. Over 40% of our patients had moderate to severe PH.

The current study was not designed to determine the prevalence of SAPH within any individual clinic. Previous reports from centers participating in the registry have found SAPH in over ten percent of all their patients⁶. At another center, right heart catheterization was performed in sarcoidosis patients with persistent dyspnea¹. Over half of the patients studied had pulmonary hypertension, with a twenty

percent of those with pulmonary hypertension having left ventricular dysfunction. In referral centers, pulmonary hypertension has been identified in about ten percent of pulmonary sarcoidosis patients ^{7;18}.

It has been noted that SAPH patients have lower FVC and DL_{CO} than other sarcoidosis patients ^{5;7;8;18;19}. In our study, there was also a significant correlation between the DL_{CO}% predicted and severity of PH (Figure 3). Overall, the median FVC was 60%, consistent with moderate restriction. There was no correlation between any of the spirometric values and severity of PH. Several screening strategies have been proposed which include use of echocardiography, DL_{CO}, 6MWD, and patient symptoms ^{8;20;21}. None of these were used in a systematic manner by the centers involved in this study. An area for future studies is how these parameters can be used in concert to risk stratify for the presence and severity of PH.

Previous studies have reported that the majority of SAPH patients have pulmonary fibrosis (Scadding stage 4) ^{4;14} based on chest x-ray changes. While pulmonary fibrosis is a recognized cause of pulmonary hypertension, a significant proportion of cases have less advanced radiologic changes ^{5;6;8;19;28}. In the current study, half the patients had stage 4 chest x-ray findings. Figure 4 demonstrates that there was no significant difference in the mPAP for different Scadding stages, although the PVR was significantly higher for stage 4 compared to stage 0 or 1 SAPH patients. Thus, our study suggests that presence of fibrosis is not essential for the development of SAPH and attests to the multifactorial nature of its etiology. One of the limitations of our study is that most patients were recruited from a tertiary sarcoidosis clinic and there may have led to patients with more advanced underlying lung disease. We also looked whether SAPH patients with extra-pulmonary disease had more severe pulmonary

hypertension. Although more than half of our patients had evidence of systemic disease, there was no difference in severity of SAPH for these patients compared to those with lung only disease.

The 6MWD was reduced in our SAPH patients compared to other sarcoidosis patients²². A reduction in 6MWD in SAPH patients has previously been reported^{22,23}. Desaturation during the 6MWD test has been proposed as a method to identify patients with SAPH⁷. There was a significant inverse correlation between 6MWD and mPAP as well as PVR (Table 3).

Several drugs have been used to treat SAPH. These include prostenoids^{17,24}, endothelin receptor antagonists^{25,26}, PDE-5 inhibitors²⁷, and combination therapy^{6,28}. Most SAPH patients were receiving PH-directed therapy at the time of entry into the study (Table 4). This is similar to the 77% of patients treated in the French registry⁴. At the time of enrollment, 84% of the non- US SAPH patients were receiving therapy for PH compared to 70% of the US patients. In reviewing drug therapy for PH 70% of the non-US patients were receiving a PDE-5 inhibitor, while only 35% of the US patients were on a PDE-5 inhibitor. The use of calcium channel blockers was significantly more common in the US sites. This may be a reflection of the previously noted overuse of channel blockers for pulmonary hypertension by US centers²⁹. A third of patients had vasoreactivity testing performed. However, the results of vasoreactivity testing were not predictive of which patients were subsequently treated with calcium channel blockers (data not shown).

There are several possible reasons for the difference in rate of treatment of SAPH for US versus non-US sites. The rate of moderate to severe PH was similar for the US and non-US sites (Table 5). The rate of

treatment was significantly higher for non-US versus US sites for both the mild and moderate to severe PH patients. The current report only captured the treatment at time of entry into the study. Patients may have subsequently been started on therapy. Also, we were unable to determine whether the decision to not treat was because of lack of insurance coverage. The higher treatment rate for the non US sites may represent the efforts of the few specialized non US centers which participated in this study. However, the recent report from France⁴ found that the overall rate of treating SAPH in France was higher than reported by our US centers.

Conclusion

This is the first study describing demographics and clinical features of a large multi-center international cohort of SAPH patients. There were few differences in the features of SAPH between the US and non-US subjects. One should always consider pulmonary hypertension as a cause of persistent dyspnea in a sarcoidosis patient. SAPH patients in the US were less likely to be receiving treatment for their PH at the time of enrollment in the study. Hopefully, the registry will also foster a greater awareness of SAPH and encourage future randomized clinical trials to help define the role of therapy for this emerging entity.

Table 1**Features of 176 patients with SAPH**

		SAPH
	N	
Number		176
Age		58 (34,81) *
Female:Male		125:51 (71%:19%) †
White/Black/Asian/Middle Eastern		57:96:5:19 (32%:55%:3%:11%)
RA, mm Hg	165	5 (0,21) *
sPAP, mm Hg	176	55 (35, 109) *
dPAP, mm Hg	175	22 (7, 65) *
mPAP, mm Hg	176	35 (25, 62) *
PAWP, mm Hg	176	10 (1,15) *
Cardiac Output	160	5.3 (2, 10.3) *
Cardiac Index	130	2.82 (1.2, 5.04) *
PVR	160	5.49 (1.85, 20.49) *
FVC % predicted	168	60 (19, 132) *
FEV ₁ % predicted	169	54 (22, 119) *
FEV ₁ /FVC %	167	74 (21, 98) *
DLCO % predicted	139	37 (13, 94) *
Chest X-ray Scadding stage ‡		
0	7	7
1	4	4
2	12	12

3	23	23
4	89	89
Six-minute walk test results *		
Distance walked (m)	142	305 (11,610) *
End of walk Borg	142	4 (0,10) *
End of walk oxygen saturation (%)	142	90 (47, 100) *
Change in saturation during walk	142	-5 (-50, 10) *

*Median (Range)

†Number (percent)

RAP - right atrial pressure; sPAP- systolic pulmonary artery pressure, dPAP – diastolic pulmonary artery pressure, mPAP - mean pulmonary artery pressure; PAWP – pulmonary artery wedge pressure; PVR – pulmonary vascular resistance; FVC – forced vital capacity; FEV₁ – forced expiratory volume at 1 second; DL_{CO} – diffusion capacity for carbon monoxide.

Table 2

Characteristics of SAPH patients: US versus non-US clinics

	US		Non US	
	N	Median (range)	N	Median (range)
Number	126		50	
Age, years		58 (37,81)		56 (34,79)
Female/Male	86/40 (68%;32%) *		39/11 (78%;22%)	
Race: White/Black/Asian/ Middle Eastern	37/86/ 4/0 (29%;68%: 3%: 0%)		20/10/1/19 (40%: 20%: 2%: 38%) □	
mPAP	126	34 (25,60)	50	36.5 (25, 62)
Cardiac Index	109	2.8 (1.2, 5.04)	21	3.01 (1.4, 4.13)
PVR	115	5.16 (1.85, 18.32)	45	6.89 (1.97, 20.49) †
FVC % predicted	118	58.5 (19, 132)	50	64.5 (28, 104)
FEV ₁ % predicted	119	52 (22, 119)	50	56.9 (15.3, 91.7)
FEV ₁ /FVC %	119	71 (27, 91)	48	79 (21, 98)
DLCO % predicted	94	37.25 (3,94)	45	36.3 (14.2,69)

mPAP - mean pulmonary artery; PVR -pulmonary vascular resistance; FVC – forced vital capacity; FEV₁ – forced expiratory volume at 1 second; DL_{CO} – diffusion capacity for carbon monoxide.

*Number (percent)

□ Differs from United States, Chi Square=64.804, p<0.0001

†Differs from United States, p=0.0079

Table 3**Correlation between six-minute walk distance and various parameters**

	Rho	p
Age	-0.144	0.0874
End of walk saturation	-0.035	0.687
Change in oxygen saturation	0.0788	0.3617
End of walk Borg	-0.243	0.0054
sPAP, mm Hg	-0.281	0.007
dPAP, mm Hg	-0.176	0.0359
mPAP mm Hg	-0.196	0.0191
PVR, Woods units	-0.292	0.0008
FVC% predicted	0.103	0.2261
FEV₁% predicted	0.09	0.2918
DL_{co}% predicted	0.38	<0.0001
Scadding stage	-0.008	0.9376

sPAP- systolic pulmonary artery, dPAP – diastolic pulmonary artery, mPAP - mean pulmonary artery mean; PVR _ pulmonary vascular resistance; FVC – forced vital capacity; FEV₁ – forced expiratory volume at 1 second; DL_{co} – diffusion capacity for carbon monoxide.

Table 4

Therapy at time of entry into registry

	US	non US
Number of Patients	126	50
	Current	Current
Epoprostenol	3 (2%) §	0
Treprostinil *	7 (6%)	0
Iloprost	1 (1%)	1 (2%)
Any prostacyclin	11 (9%)	1 (2%)
Ambrisentan	16 (13%)	3 (6%)
Bosentan	20 (16%)	13 (26%)
Macitentan	4 (3%)	2 (4%)
Any ERA	40 (32%)	18 (36%)
Sildenafil	28 (22%)	35 (70%)
Tadalafil	19 (15%)	0
Any PDE-5 inhibitor □	44 (35%)	35 (70%)
Riociguat	1 (1%)	0
Any calcium channel blocker †	21 (16.7%)	2 (4%)
No therapy **	41 (32.5%)	4 (2%)

*No patient previously on epoprostenol

§Number (percent of total for group US or non-US)

□ Chi square=17.704, p<0.0001.

† Chi square=4.002, p=0.0454

** Chi square=11.26, p=0.0008

Table 5

Comparison of treatment for US and non-US patients with mild versus moderate-severe pulmonary hypertension *

	Mild Pulmonary Hypertension PA mean \leq 35 mm HG			Moderate-severe Pulmonary Hypertension PA mean > 35 mm Hg	
	Total number	No Therapy		Total Number	No Therapy
US	71	26 (37%)		55	15 (27%)
non US	24	3 (12%) *		26	1 (4%) □

*Differs from US, Chi square=3.849, p=0.0498.

□ Differs from US, Chi square=4.724, p=0.0297.

Figure Legend

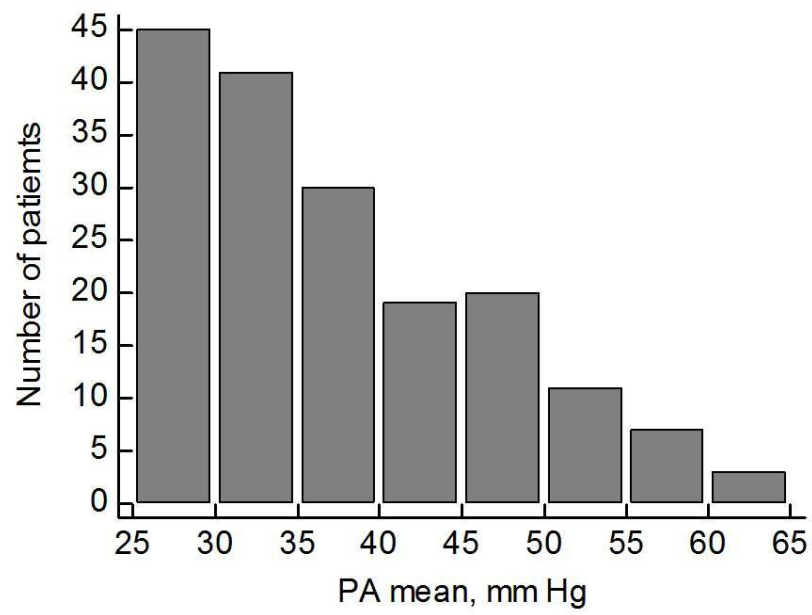
- Figure 1 Flow sheet of 216 patients in the sarcoidosis associated pulmonary arterial hypertension registry. Based on right heart catheterization measurements, 176 patients were identified with a pulmonary artery mean (mPAP) ≥ 25 mm Hg and a pulmonary capillary wedge (PAWP) of 15 mm Hg or less.
- Figure 2 Histogram of mPAP (Figure 2A) and PVR (Figure 2B) for the whole population.
- Figure 3 Comparison between DLCO percent predicted and mPAP (Figure 3A, $Rho=-0.228$, $p=0.0068$) and PVR (Figure 3B, $Rho=-0.362$, $p<0.0001$).
- Figure 4 Comparison between the Scadding¹⁴ chest x-ray stage and the mPAP (Figure 4A) and PVR (Figure 4B). There was no difference between groups for mPAP. There was a significant difference between PVR for different chest x-ray patterns (Kruskal-Wallis, $p=0.033507$), with stage 4 being significantly different from those who were stage 0 or 1 ($p<0.05$ for both comparisons).
- Figure 5 Relative frequency of oxygen desaturation detected by oximetry during six minute walk of 142 patients.
- Figure 6 Correlation between DLCO percent predicted and 6 minute walk distance ($\rho=0.380$, $p<0.0001$).

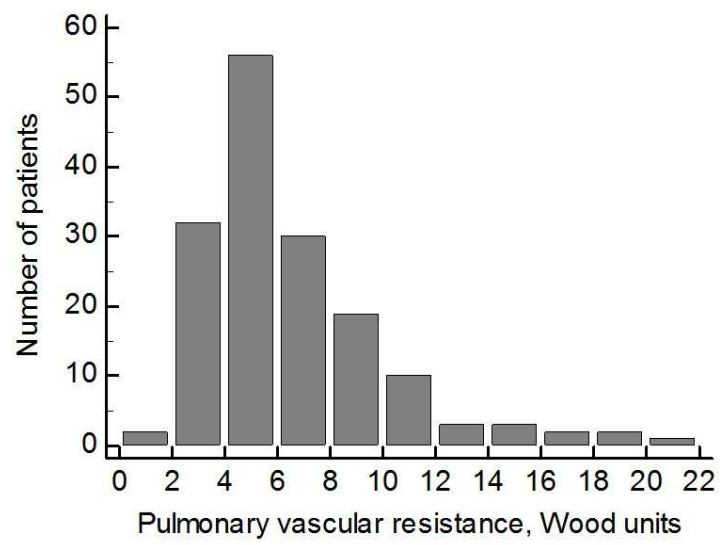
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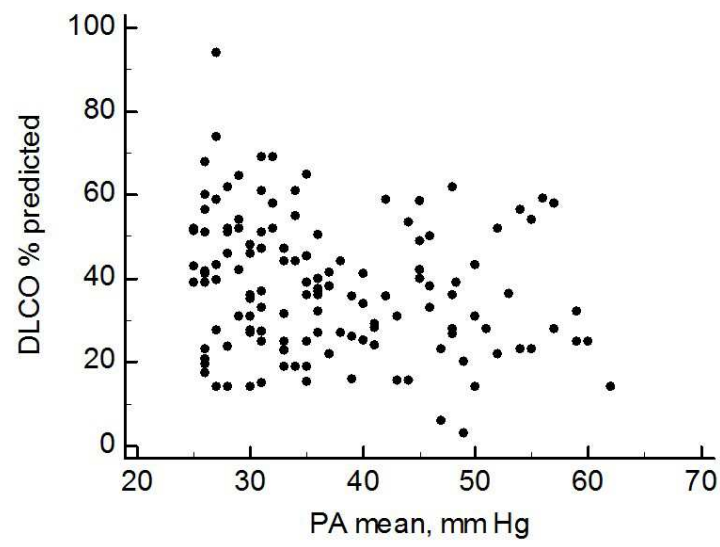
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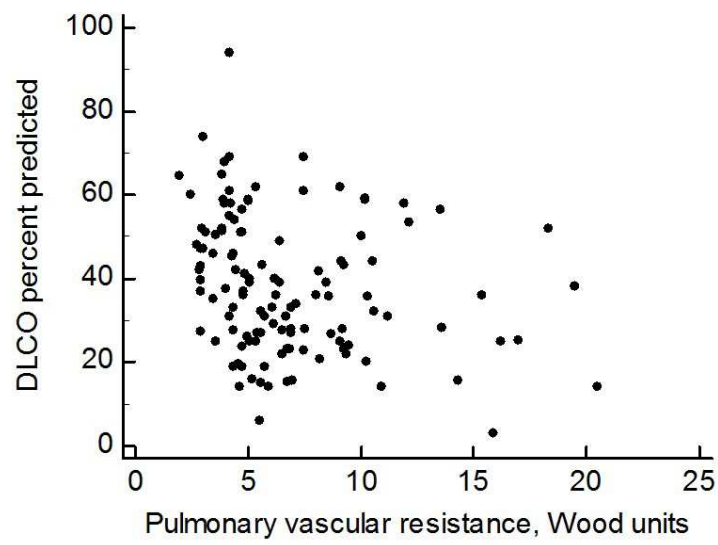
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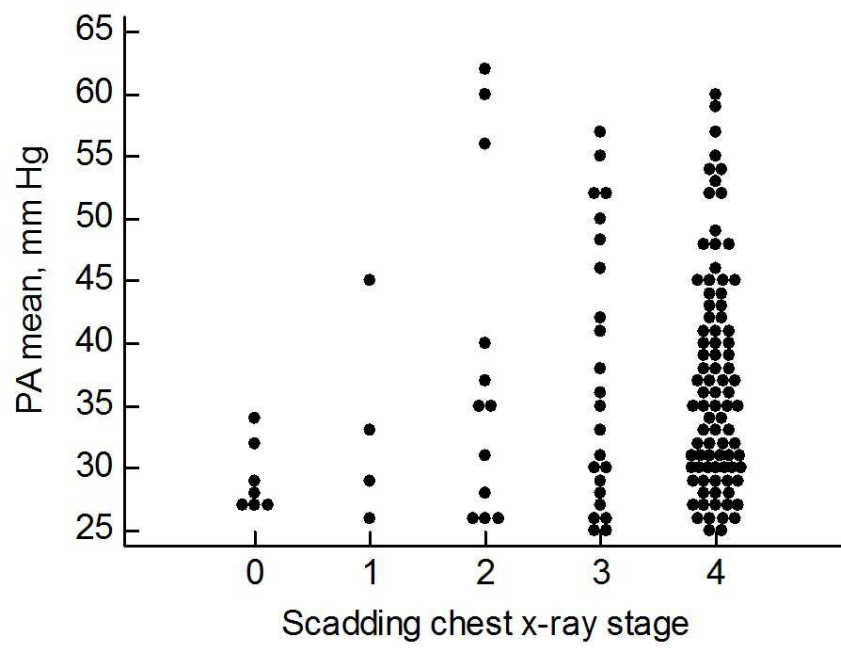
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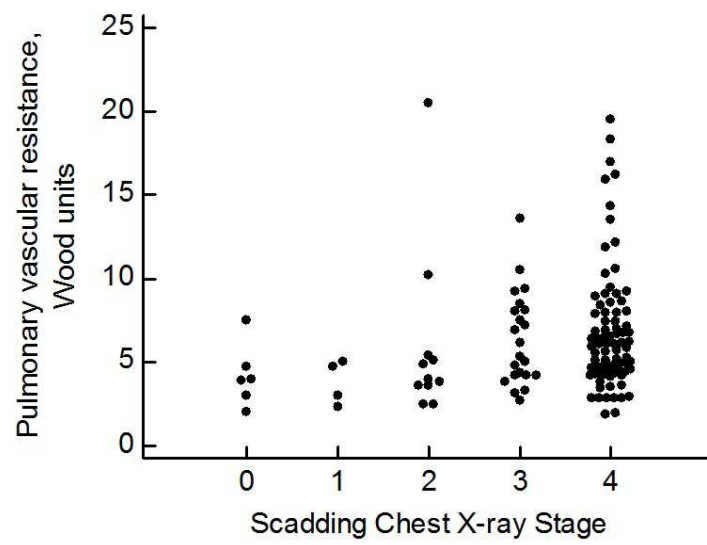


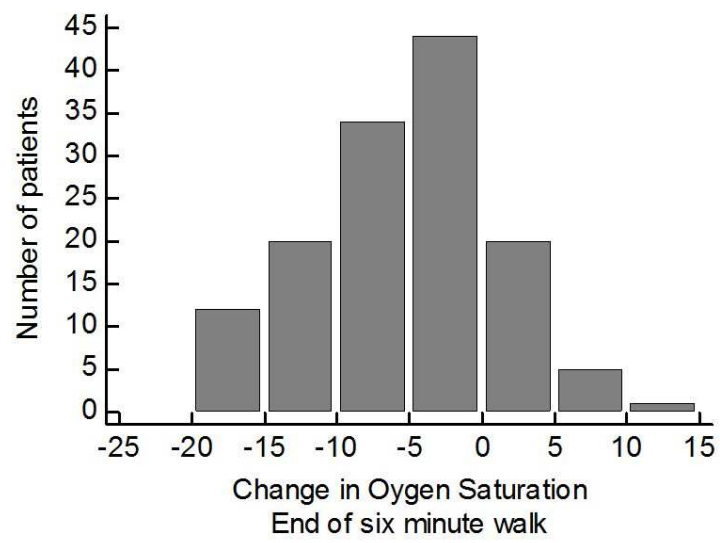


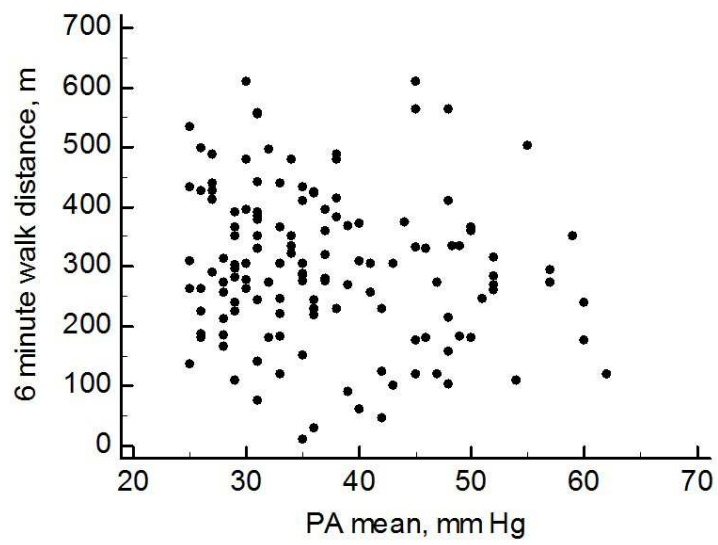


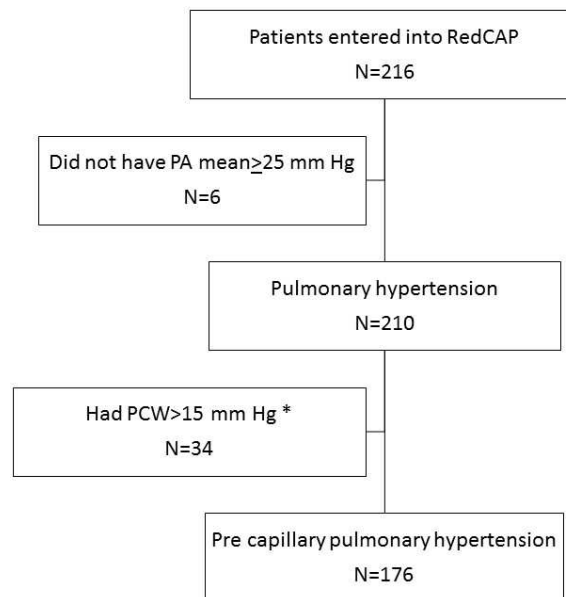












Highlights

- Multi-national study of 176 sarcoidosis associated pulmonary hypertension patients
- Similar clinical features across US, Europe, and Middle East
- Pulmonary vascular resistance was higher in patients with pulmonary fibrosis
- There was a correlation between DLCO and level of pulmonary hypertension
- Pulmonary hypertension was more likely to be treated in Europe than US

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